Lymphoma

Introduction

A lymphoma is any tumor of lymphocytes that occurs outside the bone marrow, usually contained by some organ. Lymph, lymphocytes; oma, mass. But that's not how we want you thinking. There are technically three categories of lymphomas: B-cell lymphomas, T-cell lymphomas, and plasma cell dyscrasias. This lesson is about B-cell lymphomas.

The B-cell lymphomas discussed in this lesson are separated from the B-cell lymphomas discussed in Proliferation #5: *Plasma Cell Dyscrasias*. The separation is not arbitrary, though is very different from typical pathology textbooks. The B-cell lymphomas in this lesson all proliferate, but **do not secrete immunoglobulin**, in contrast to the plasma cell dyscrasias which have secretion of immunoglobulin as their primary pathogenesis. You don't get swollen lymph nodes in multiple myeloma (a plasma cell dyscrasia), but you do in the lymphomas of this lesson.

Because there are B-cell lymphomas there must also be T-cell lymphomas. When you hear "lymphoma," you should immediately think of the "B-cell lymphoma that occurs in germinal centers." Only when someone specifically says "T-cell lymphoma" should you consider anything T-cell related. We close this lesson with honorable mentions from the T-cell lymphomas category. They are considered extremely low yield.

So, we discuss B-cell lymphomas. There are two types. The main distinction between lymphomas is going to be whether they are Hodgkin's ($CD15^+/CD30^+$) lymphoma or non-Hodgkin's lymphomas. We start off with the common diagnostic pathway, then discuss each lymphoma in detail.

Lymphoma Diagnosis and Staging

Lymphomas present with painless lymphadenopathy. A **painless fixed** node is more likely to be malignancy than a painful mobile node. Think of a cancer slowly growing, reaching tendrils out of the node, grabbing hold of the nearby tissue. Because it grows slowly, the capsule has time to stretch, so is not painful. Because its tendrils dig into nearby tissue, it is immobile, fixed in position. Compare that to a lymph node expanding rapidly because abundant antigen has been identified. Rapid expansion of the node from germinal center activity stretches the capsule and causes pain. With only normal, healthy cells doing what they are supposed to do, no tendrils exit the capsule into nearby tissue. And after the infection is taken care of, the node resumes its normal size. **Painful mobile** nodes are likely to be **infection**.

When you identify a possibly malignant node, an **excisional biopsy** is required. A fine-needle aspiration is less invasive (a needle through the skin, compared to surgical exploration and dissection), but inadequate to make the diagnosis. It is the most common error students make when dealing with lymphoma. A fine-needle aspiration is used in the diagnosis of many cancers. It is never the right answer in lymphoma. The excisional biopsy is required to make the diagnosis because the **nodal architecture** makes the diagnosis. You need to take the node out, splay it open, section it, and look at its overall structure. Especially in the case of Hodgkin's lymphoma, where normal cells make up 90% of the tumor, a fine-needle aspiration is more likely to miss the cancer cells than catch one.

When the diagnosis of lymphoma is made, whether it is Hodgkin's or non-Hodgkin's, staging is done with imaging. The combination of **CT chest/abdomen/pelvis** and **PET scan** reveals the number and location of nodes involved. The term "B symptoms," used in reference to several other diseases (such as TB), comprises **fever, night sweats,** and **weight loss**. The term "B symptoms" originated in the staging of lymphoma. Staging is by numbers and a letter. Stage A means "no B symptoms." Stage B means "with B symptoms." The absence of B symptoms portends a better prognosis. Staging is as follows:

STAGE	NUMBER OF NODES	RELATIVE TO DIAPHRAGM
1	1	n/a
2	≥ 2	Same side
3	≥ 2	Both sides
4	Metastatic to other organs	

MODIFIER	B SYMPTOMS
A	Absent
B	Present

Table 4.1: Staging of Lymphomas.

Hodgkin's vs. Non-Hodgkin's

Hodgkin's lymphoma (HL) is a unique B-cell lymphoma caused by Reed-Sternberg cells. As discussed in detail below, these cells are $CD15^+/CD30^+$ and negative for all other B-cell and T-cell markers. Reed-Sternberg cells are not present in non-Hodgkin's lymphomas (NHL; note that our grammatically singular "NHL" refers to the plural non-Hodgkin's lymphomas).

HL tends to spread contiguously, anatomically, following the lymphatic anatomy. NHL are sporadic and can occur anywhere. Their spread is noncontiguous.

HL responds to ABVD and radiation. NHL does not. NHL responds to R-CHOP. HL does not. You do not need to memorize treatment regimens for cancers. You should be aware that rituximab is a monoclonal antibody against CD20. Since NHL is caused by regular B cells that do express CD20, rituximab is effective against NHL. Because HL is caused by abnormal B cells that do not express CD20, rituximab is ineffective against HL. Notice that both treatments involve an alkylating agent (doxorubicin, daunorubicin) and a vinca alkaloid (vincristine). Radiation and alkylating agents are what are responsible for secondary malignancies years after cure of the original lymphoma.

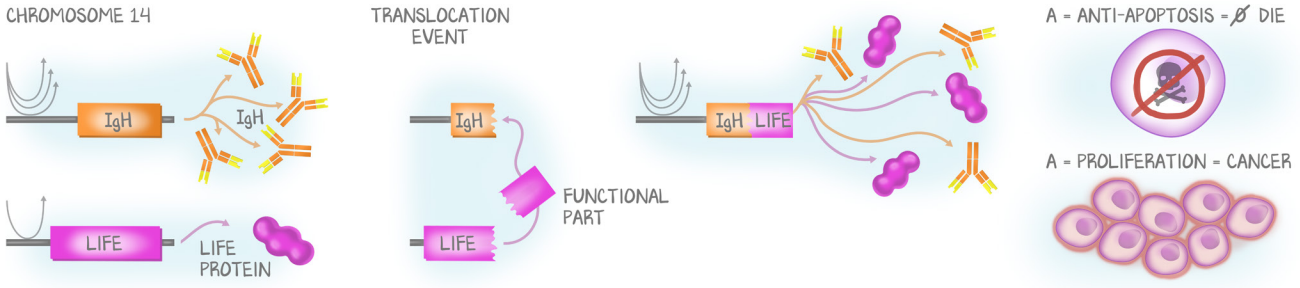
HODGKIN'S		FEATURE	NON-HODGKIN'S	
Adriamycin® (doxorubicin)	Single node or chain	Location and Number	Multiple and separate	**R**ituximab
Bleomycin	Anatomic, contiguous	Spread	Hematogenous, noncontiguous	**C**yclophosphamide
Vincristine	Not involved	Mesentery Nodes	Involved	**H**ydroxy-daunorubicin
Dacarbazine	Rare	Extranodal Presentation	Common	**O**ncovin ® (vincristine)
Radiation				**P**rednisone

Table 4.2: Comparison of Lymphomas

We want you to learn that there is a Hodgkin's lymphoma (the "classical" type) with several histologic variations, and many non-Hodgkin's lymphomas, each with their own pathogenesis, presentation, and histologic appearance.

Non-Hodgkin's Lymphomas

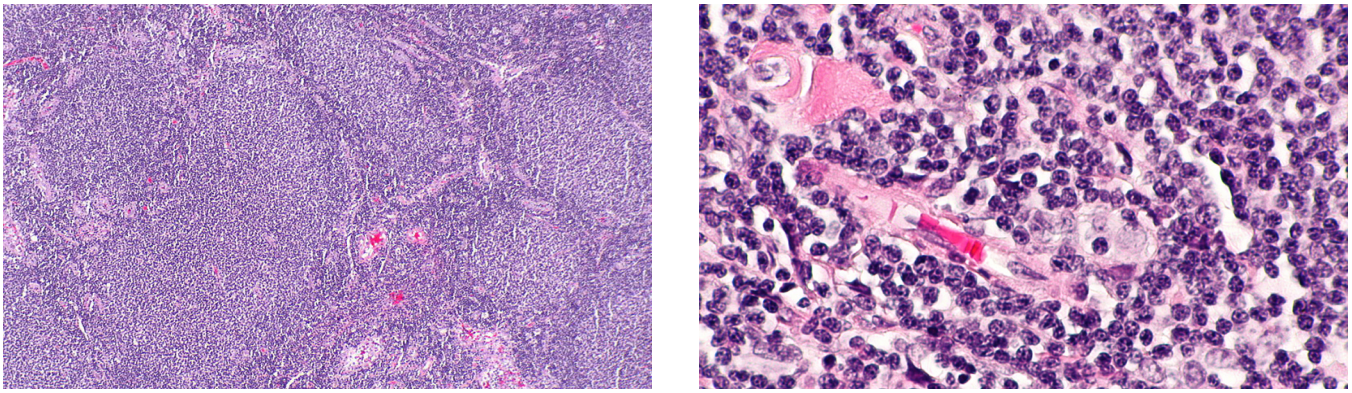
Non-Hodgkin's lymphomas are commonly associated with **EBV latent infection** and subsequent **transformation**. Whereas Hodgkin's lymphoma is characterized by reliable mutations and CD marker expressions, the non-Hodgkin's lymphomas each have their own unique findings. The common thread between most of the non-Hodgkin's lymphomas is a translocation between either an anti-apoptosis gene or a proliferation gene and the **Ig heavy-chain gene**. Being B cells in origin, the Ig heavy chain naturally has increased genetic expression. When a translocation event brings an anti-apoptosis or proliferation gene under the control of the Ig heavy-chain gene's promoter, excess expression of "live" signal results in proliferation and accumulation of more mutations, which leads to advancing disease. The Ig heavy-chain gene is on **chromosome 14**. You will see, rather than memorizing the full translocation, you need only memorize the one gene's chromosome that translocates with chromosome 14.



LYMPHOMA	TRANSLOCATION	SHORT	GENE
Follicular	t(14;18)	18	BCL-2
DLBCL	N/A	N/A	BCL-6
Burkitt's	t(8;14)	9	c-Myc
Mantle cell	t(11;14)	11	Cyclin D1
Marginal zone	t(11;18)*	N/A	N/A

Figure 4.1: Non-Hodgkin's Lymphoma
Mechanism of translocation of one gene to the control of the promoter of the IgG heavy-chain gene, demonstrating increased expression of anti-apoptosis (survival but no growth) or pro-proliferation (rapid growth) genes leading to cancer.

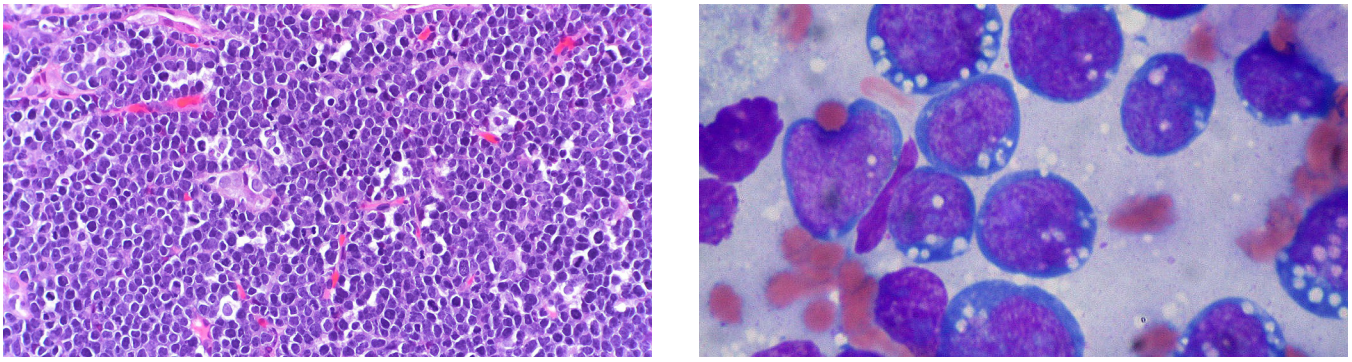
Follicular Lymphoma. Follicular lymphoma is caused by a translocation between the **BCL-2** gene on chromosome 18 and the IgH gene on chromosome 14, **t(14;18)**. BCL-2 is anti-apoptotic. Follicular lymphoma cells don't apoptose, but there is also no proliferation signal. It is **indolent,** slow growing, very hard to cure, but also very easy to live with. A low mitotic rate means that it is not vulnerable to chemotherapy or radiation. But a low mitotic rate also means that it does not grow quickly or spread. It is a germinal-center B cell gone haywire. Normal germinal-center B cells do not express BCL-2—they are supposed to die off, letting only those B cells with the highest affinity for antigen proliferate. A germinal center, a follicle, is surrounded by mantle cells expressing BCL-2 and a mass of B cells proliferating and building immunoglobulin that does not express BCL-2. In follicular lymphoma, a malignancy caused by the cells within the germinal center, within the follicle, all of the cells express BCL-2. On histology, follicular lymphoma looks to have an increased number of scattered germinal centers (or follicles). Although incurable, follicular lymphoma follows an indolent course. Survival is **not improved by aggressive chemotherapy**. However, as patients become symptomatic, palliative treatment with **rituximab** (anti-CD20) can improve quality of life. **Half** will progress to diffuse large B-cell lymphoma.



(a) (b)

Figure 4.2: Follicular Lymphoma (Lymph Node)
(a) Nodular aggregates of lymphoma cells are present throughout lymph node. (b) At high magnification, small lymphoid cells with condensed chromatin and irregular or cleaved nuclear outlines (centrocytes) are mixed with a population of larger cells with nucleoli (centroblasts).

Burkitt's Lymphoma. Burkitt's lymphoma is caused by a translocation between the **c-Myc** gene on chromosome 8 and the IgH gene on chromosome 14, **t(8;14)**. c-Myc, sometimes seen as MYC, is a master transcriptional regulator. It is a transcription factor that upregulates cyclin expression, upregulates expression of rRNA and proteins, upregulates metabolism, upregulates BCL-2, downregulates p21, and accelerates p53 degradation. It isn't just one gene that does one thing. It is one gene that tells all of the cellular machinery to build and proliferate. Burkitt's lymphoma is therefore the fastest-growing cancer in humans. All Burkitt's lymphomas look the same under the microscope, but there are three clinical courses involving Burkitt's lymphoma. There is an **endemic African** form that commonly occurs in the lymph nodes of the **mandible** and abdominal viscera. There is an **aggressive** form that occurs in individuals infected with HIV. This is not thought to be general immunocompromise from AIDS accelerating cancer. Simply being infected with HIV, even with a normal CD4 count, greatly accelerates the disease course. The **sporadic** nonendemic variant is what we see in the United States. It involves mostly extranodal tissues, especially the **ileocecum** and **peritoneum**. Burkitt's lymphoma commonly occurs in **children**, and is **easily cured**, given its high mitotic rate. The adult form associated with HIV has a dismal prognosis. Pathology reveals a **starry sky appearance**. This has been propagated throughout textbooks and review resources. Students are left wondering if this means the histology looks like the Van Gogh painting *Starry Night*, or if it means, literally, a sky at night with stars in it. I'm not sure who thinks the sky looks like the slides in the following images, but the term "starry sky appearance" describes a bunch of darkly stained cells with little cytoplasm packed really tightly together (supposed to be the blackness of space), interspersed with puffy white cells with abundant cytoplasm (supposed to be the stars). Those puffy white cells are called **tingible body macrophages**. In normal germinal centers, there is massive proliferation of B cells. Only those with the highest affinity for antigen proliferate. The others die. Dying cells are cleaned up by macrophages. Tingible body macrophages are normally seen in germinal centers. In Burkitt's lymphoma, there is so much proliferation, so much metabolic activity, that even malignant cells die. Dying cells are cleaned up by macrophages. The "sky" is all cancer cells. The "stars" are macrophages clearing dead cancer cells. Why not just say that instead of confusing everyone with that the hell "starry sky" means?

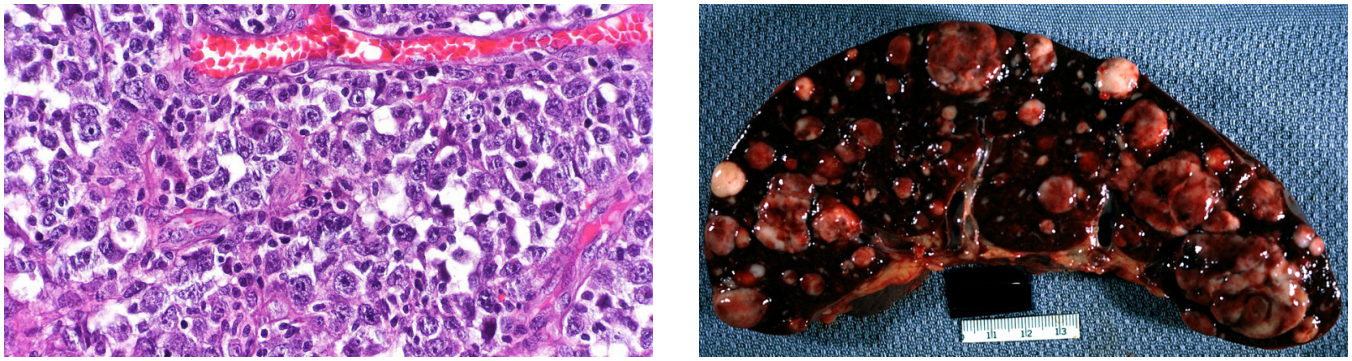


(a) (b)

Figure 4.3: Burkitt's Lymphoma
(a) At low power, numerous pale tingible body macrophages are evident, producing a "starry sky" appearance. (b) At high magnification, tumor cells have multiple small nucleoli and high mitotic index. The lack of significant variation in nuclear shape and size lends a monotonous appearance.

Mantle Cell Lymphoma. Mantle cell lymphoma is caused by a translocation between the **cyclin D_1** gene on chromosome 11 and the IgH gene on chromosome 14, **t(11;14)**. Cyclin D_1 is the final signal that allows passage through the retinoblastoma checkpoint between G_1 and S phase of the cell cycle. Expression of cyclin D_1 guarantees progression through that checkpoint. The IgH genes lack somatic hypermutation, suggesting that this is a malignancy originating from a naïve B cell. CD19, CD20, and IgM are found on the surface. Even though this is a B cell, mantle cell lymphoma also expresses **CD5.** This is not a good lymphoma to have. It is aggressive and incurable, given current therapies. At the time of diagnosis, there is usually **diffuse lymphadenopathy**, and half already have blood involvement (so technically a leukemia).

Diffuse Large B-cell Lymphoma. DLBCL is genetically homogeneous and does not have a translocation event associated with it. It is the **most common NHL** in the United States. Follicular lymphomas that become DLBCL demonstrate t(14;18) and express BCL-2. Over half of DLBCL patients overexpress **BCL-6**. For test-taking purposes, learn DLBCL = BCL-6. For life, learn that DLBCL requires immunohistochemistry to determine the biology of the cancer before choosing treatment. DLBCL typically presents as a rapidly enlarging mass at a nodal or extranodal site. It can arise virtually anywhere in the body. The Waldeyer's ring, the oropharyngeal lymphoid tissue that includes the tonsils and adenoids, is involved commonly. Primary or secondary involvement of the liver and spleen may take the form of large destructive masses. The common histologic finding is, in line with its name, extremely **large cell size** (usually four to five times the diameter of a normal lymphocyte).



(a) (b)

Figure 4.4: DLBCL
(a) Tumor cells have large nuclei, open chromatin, and prominent nucleoli. (b) Diffuse large B-cell lymphoma involving the spleen. The isolated large mass is typical. In contrast, indolent B-cell lymphomas usually produce multifocal expansion of white pulp.

Marginal zone lymphomas break the mold. They are not caused by a translocation involving the heavy chain. They are caused by a translocation of chromosomes 11 and 18. While marginal zone lymphomas can occur in lymph nodes, you should learn this lymphoma as being the **extranodal** lymphoma that arises from **chronic inflammation**. Marginal zone lymphomas arise near tissues with chronic inflammatory diseases (Hashimoto's thyroid gland, Sjogren's salivary gland) or in tissues with chronic infections (such as **MALTomas** caused by H. pylori **gastritis**). They remain localized for prolonged periods, spreading systemically only very late in the disease course. If the inflammation that is inducing them is removed (we cure the *H. pylori* infection) the lymphoma regresses. That all sounds like extranodal marginal zone lymphomas are just a continuum between reactive lymphoid hyperplasia on the one hand, and cancer only very late in the disease course. This makes a lot of sense. Ongoing inflammation **appropriately** induces proliferation. Ongoing proliferation from normal trophic signals provides more opportunity for malignant transformation. And guess which mutations malignant marginal zone lymphomas acquire if the inflammation isn't removed? t(11;18), t(11:14), and t(14;18). Treating *H. pylori* treats stomach cancer.

Hodgkin's Lymphoma

We want you learning only the "classical" Hodgkin's lymphoma, as if there were only one Hodgkin's lymphoma and not multiple subtypes. You should know that there are five histologic variants, four of them following the same clinical progression (together they are the classical Hodgkin's lymphoma), and a fifth that is effectively its own disease. Knowing that, learn classic Hodgkin's only.

Hodgkin's disease is caused by **Reed-Sternberg cells** (RS cells). RS cells are lymph node B cells that have already undergone isotype switching and somatic hypermutation, and so HL is a cancer of memory B cells. Despite having the genes of mature B cells, the expression of those genes in RS cells is essentially nonexistent. They do not make immunoglobulin in any form, do not have antigen receptors, and do not release antibodies. These cells release factors that induce the accumulation of reactive lymphocytes, macrophages, and granulocytes, which typically make up greater than 90% of the tumor cellularity. The tumor is NOT full of monoclonal expansion of a malignant cell, but instead full of normal leukocytes summoned by the all-seeing Eye of Sauron RS cell.

Activation of the transcription factor **NF-κB** is a common event in classical Hodgkin's. NF-κB is usually activated by the RANK (receptor activator of nuclear factor κB) and the NF-κB pathway leads to cell proliferation. Activation of NF-κB happens through unknown non-EBV mechanisms and through several Epstein-Barr virus (EBV) mechanisms. In an acute EBV infection, there are B cells that resemble the appearance of RS cells. Latent infection with EBV results in malignant transformation. It is hypothesized that EBV upregulation of NF-κB rescues crippled germinal center B cells that cannot express immunoglobulins from apoptosis.

The RS cell is in a lymph node where trophic signals are being released all the time. The RS cell then recruits additionally inflammatory cells and tricks those normal healthy cells into feeding it growth factors. The RS cell inhibits cytotoxic immune response with the release of interleukin-10, increases expression of eosinophils with IL-5 (which in turn stimulates the RS cell with CD30L), and stimulates the Th2 response (which in turn stimulates the RS cell with CD40L). This **crosstalk** results in an accumulation of cells, with subsequent lymph node swelling. We've withheld much of the crosstalk. The numerous variations in which inflammatory cells accumulate around the RS cells determine the histologic subtype—mixed cellularity, lymphocyte predominant, and lymphocyte depleted.

RS cells are **$CD15^+/CD30^+$** and **negative for all other lymphocyte markers** (no T-cell markers, no B-cell markers, and no CD45, the leukocyte common antigen). You need to be able to identify RS cells on a slide. There will be a test question about classical Hodgkin's disease, you will be given a slide with an

RS cell on it, and it will give you the answer on the test. **Visualizing RS cells is insufficient for clinical diagnosis.** There must be immunohistochemistry confirmation of $CD15^+/CD30^+$ to make the diagnosis of Hodgkin's. This is because the treatment for classical Hodgkin's is so good at curing Hodgkin's (70% cure, 90% disease-free at 5 years), but not anything else, that the diagnosis must be certain.

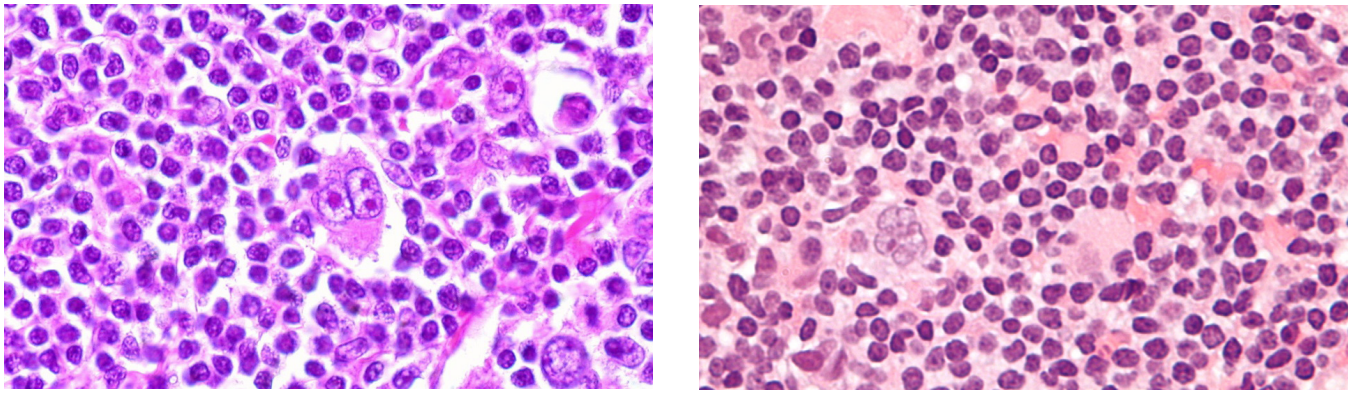
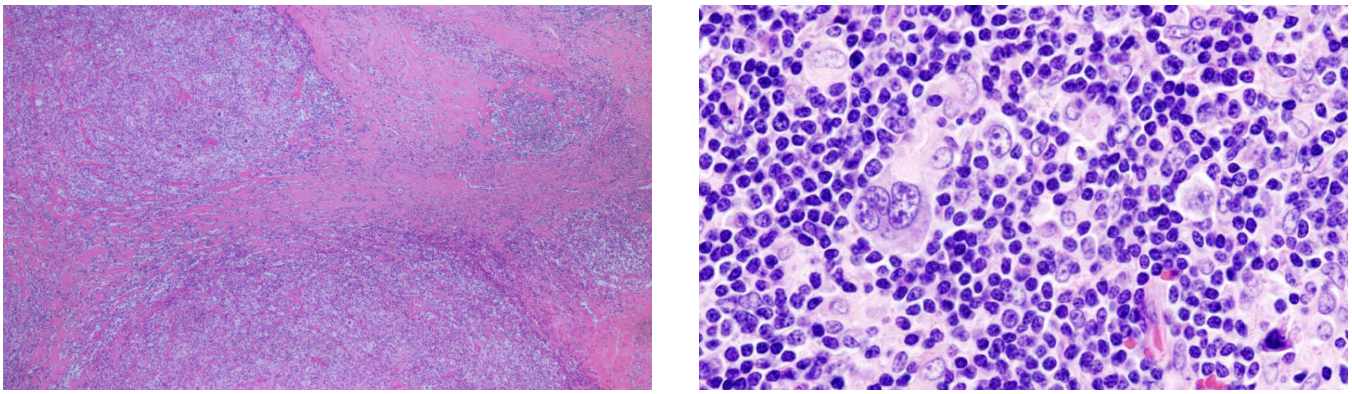


Figure 4.5: Reed-Sternberg Cells
RS cell with two nuclear lobes, large inclusion-like nucleoli, and abundant cytoplasm, surrounded by lymphocytes, macrophages, and an eosinophil.

Diagnostic Reed-Sternberg cells are large cells (45 μm in diameter) with multiple nuclei or a single nucleus with multiple nuclear lobes, each with a large inclusion-like nucleolus about the size of a small lymphocyte (5 to 7 μm in diameter). They will be surrounded by other inflammatory cells. The most common histologic subtype is **nodular sclerosis**. The most likely to demonstrate RS cells is **mixed cellularity type**.



(a) **(b)**

Figure 4.6: Hodgkin's Lymphoma
(a) Nodular sclerosing—very low magnification of nodular sclerosis type showing the bands of collagen encircling islands of lymphocytes. (b) Mixed cellularity binucleate Reed-Sternberg cell is surrounded by reactive cells, including eosinophils (bright red cytoplasm), lymphocytes, and histiocytes.

While NHLs frequently occur at extranodal sites and spread in an unpredictable fashion, HL arises in a **single node** or **chain of nodes** and has a **contiguous anatomical spread.** The spread of HL is remarkably stereotyped: nodal disease first, then splenic disease, hepatic disease, and finally involvement of the marrow and other tissues. Staging is the same for Hodgkin's as it is for NHL, as discussed above.

Treatment is with ABVD and radiation. ABVD combines trade and generic names. You will never be asked to choose a regimen for a malignancy. You should be familiar with ABVD.

T-Cell Lymphomas

Most T-cell lymphomas are lumped together into a wastebasket class, "Unspecified." There are no morphologic or pathogenic similarities to most T-cell lymphomas. And while there are more than we are going to share with you that have a designated disease name and presentation, the only two we think you should learn are adult T-cell lymphoma and mycosis fungoides/Sézary syndrome.

Adult T-cell leukemia/lymphoma is a neoplasm of **CD4 T-helper cells** observed in adults infected by human T-cell leukemia retrovirus type 1 (**HTLV-1**). This cancer is caused by this virus. This virus causes this cancer. Never again will either be mentioned. Most patients present with rapidly progressive disease that is fatal within months to 1 year despite aggressive chemotherapy. It occurs in regions where HTLV-1 is endemic—**Japan**, West Africa, and the **Caribbean**. It is a sexually transmitted disease. Common findings include skin lesions, generalized lymphadenopathy, hepatosplenomegaly, peripheral blood lymphocytosis, and hypercalcemia.

Cutaneous T-cell lymphoma/leukemia is another neoplasm of **CD4 T-helper cells.** These CD T-helper cells happen to make their **home in skin**. Mycosis fungoides is the cutaneous-only version of the disease. It presents with erythematous plaques or patches which appear autoimmune, but **do not heal**. A biopsy reveals intraepidermal neoplastic cell aggregates called Pautrier's microabscesses. Sézary syndrome is **skin and leukemia**, where a blood smear will show Sézary cells with **cerebriform nuclei**.